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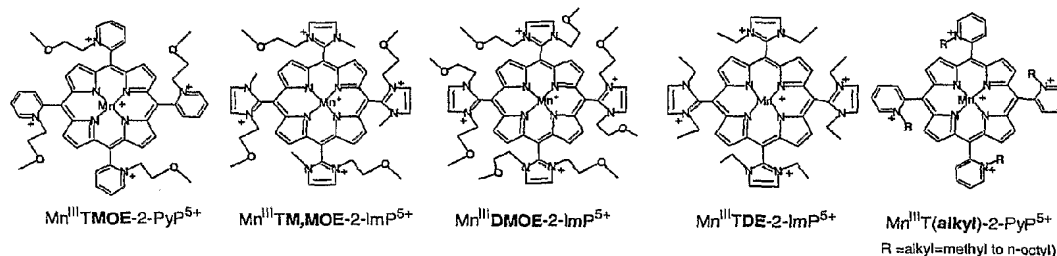
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(54) Title: SUBSTITUTED PORPHYRINS



Structures of the Mn(III) porphyrins studied

(57) Abstract: To improve bioavailability of the catalytic metalloporphyrin-based SOD mimics Mn(III) 5,10,15,20-tetrakis[*N*-ethylpyridinium-2-yl]porphyrin (MnTE-2-PyP⁵⁺) and Mn(III) 5,10,15,20-tetrakis[*N,N'*-diethylimidazolium-2-yl]porphyrin (MnTDE-2-ImP⁵⁺), three new Mn(III) porphyrins, bearing oxygen atoms within side chains, were synthesized and characterized: Mn(III) 5,10,15,20-tetrakis[*N*-(2-methoxyethyl)pyridinium-2-yl]porphyrin (MnTMOE-2-PyP⁵⁺), Mn(III) 5,10,15,20-tetrakis[*N*-methyl-*N'*-(2-methoxyethyl)imidazolium-2-yl]porphyrin (MnTM,MOE-2-ImP⁵⁺) and Mn(III) 5,10,15,20-tetrakis[*N,N'*-di(2-methoxyethyl)imidazolium-2-yl]porphyrin (MnTDMOE-2-ImP⁵⁺). The catalytic rate constants for O₂ dismutation (and the related metal-centered redox potentials vs NHE) for the new compounds are: log k_{cat} = 8.04 ($E_{1/2}$ = +251 mV) for MnTMOE-2-PyP⁵⁺, log k_{cat} = 7.98 ($E_{1/2}$ = +356 mV) for MnTM,MOE-2-ImP⁵⁺ and log k_{cat} = 7.59 ($E_{1/2}$ = +365 mV) for MnTDMOE-2-ImP⁵⁺. At 30 μM levels none of the new compounds were toxic, and allowed SOD-deficient *E. coli* to grow nearly as well as wild type. At 3 μM levels, the MnTDMOE-2-ImP⁵⁺, bearing an oxygen atom within each of the eight side chains, was the most effective and offered much higher protection than MnTE-2-PyP⁵⁺, while MnTDE-2-ImP⁵⁺ was inefficient. These new porphyrins were compared to Mn(III) *N*-alkylpyridylporphyrins. While longer-chain *n*-alkyl members of the series exerted toxicity at higher concentration levels, they were very effective at submicromolar levels. Thus, 0.3 μM Mn(III) tetrakis[*N*-*n*-hexyl-pyridinium-2-yl]porphyrin and its *n*-octyl analogue offered the same level of protection as did ≥ 10 μM methyl and ethyl porphyrins. The k_{cat} of methyl and *n*-octyl porphyrins are identical, but *n*-octyl is -10-fold more lipophilic. Therefore, the 30-fold improvement in bioavailability appears to be due to the increase in lipophilicity. MnTDMOE-2-ImP⁵⁺ and longer-chain Mn(III) *N*-alkylpyridylporphyrins may offer better treatment for oxidative stress injuries than the previously studied MnTE-2-PyP⁵⁺ and MnTDE-2-ImP⁵⁺.



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